**TICAGRELOR AND STATIN HAVE SYNERGISTIC EFFECTS ON MYOCARDIAL PROTECTION AGAINST ISCHEMIA-REPERFUSION INJURY**

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*Background*: In addition to P2Y12 receptor antagonism, ticagrelor (TIC) inhibits the equilibrative- nucleoside-transporter-1 (ENT1) and thereby, adenosine cell re-uptake. Prior data show that TIC limits infarct size (IS) in non-diabetic rats and that the effect is adenosine dependent. Statins, via ecto-5’ nucleotidase activation, also increase extracellular adenosine levels and has also been shown to limit IS. Hypothesis: By inhibition of its metabolism and enhancing its production, TIC and rosuvastatin (ROS) have synergistic effects on myocardial adenosine levels, and therefore, on IS.

*Methods*: Male obese ZDF rats (ZDF-Leprfa/Crl) developed type-2 diabetes after feeding with Purina #5008. Rats received: water (control), TIC (150mg/kg/d), prasugrel (PRAS, 7.5mg/kg/d), ROS (5 mg/kg/d), TIC+ROS and PRAS+ROS for 3d by oral gavage. Two additional groups received, control and TIC+ROS in combination with CGS15943 (CGS, an A2A/A1 antagonist, 10 mg/kg i.p. 1h before coronary occlusion). On day 4, sixteen hours after the last dose, rats were subjected to 30min coronary artery occlusion Area at risk (AR) was assessed by blue dye and IS by TTC 24h after reperfusion.

*Results*: (expressed as mean±standard error): Fasting glucose levels were comparable among groups (p=0.155). Platelet aggregation was 51.2±2.1% in the control group and equally inhibited by TIC (25.1±1.6%) and PRAS (25.3±1.3%). IS (% of the AR) was significantly reduced with both ROS (31.3±1.2%) and TIC (29.5±2.6%) vs. control (52.6±1.9%), whereas PRAS had no effect (51.8±2.2%). IS was further reduced by the combination, TIC+ROS (20.8±1.8%; p<0.001 vs. control; p=0.014 vs. ROS; p=0.076 vs. TIC), whereas no additive effect was present in the PRAS+ROS combination (39.2±2.2%; p=0.139 vs. ROS alone). CGS alone had no effect on IS (52.5±2.8%), but it completely reversed the effect of TIC+ROS (51.6±2.1%).

*Conclusions*: Ticagrelor, but not prasugrel, augments the IS-limiting effects of rosuvastatin. The protective effect is completely reversed by adenosine receptor antagonism, suggesting an adenosine mediated effect.